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सत्यमेव जयते

INTELLECTUAL PROPERTY INDIA

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY,
PATENT OFFICE, DELHI BRANCH,
W - 5, WEST PATEL NAGAR,
NEW DELHI - 110 008.

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application*** *and* ***Complete Specification*** *filed in connection with Application for Patent No.* ***805/Del/2003*** *dated* ***16th June 2003.***

Witness my hand this 8th day of July 2004.

(S.K. PANGASA)
Assistant Controller of Patents & Designs

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

Drug

A61K9/20

0805-03

FORM 1

16 JUN 2003

THE PATENTS ACT, 1970

(39 of 1970)

Govt. of India Patent Office, New Delhi Received Rs. 3500/- in cash. Cheque/M.O./T.P.O./D.D. on 16 JUN 2003 Vide Entry No. 467 in the Register of Valuables ..... Cashier

APPLICATION FOR GRANT OF A PATENT

(See Sections 5(2), 7, 54 and 135; and rule 39)

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"A PROCESS FOR THE PREPARATION OF CONTROLLED RELEASE TABLETS OF METFORMIN"**

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. MANISH CHAWLA
b. RAJEEV SINGH RAGHUVANSHI
c. ASHOK RAMPAL

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. We claim the priority from the application(s) filed in convention countries, particulars of which are as follows:

Country	:	**India**
Application No.	:	**1134/DEL/2001**
Date of Application	:	**November 06, 2001**

5. We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which we are the applicant: **NOT APPLICABLE**

6. We state that the application is divided out of our application, the particulars of which are given below and pray that this application deemed to have been filed on ..... Under section 16 of the Act. **NOT APPLICABLE**

7. That we are the assignee or legal representatives of the true and first inventors.

8. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18, Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana). INDIA.

9. Following declaration was given by the inventors or applicants in the convention country:

We, MANISH CHAWLA, RAJEEV SINGH RAGHUVANSHI, ASHOK RAMPAL of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention or applicant in the convention country declare that the applicant herein, **Ranbaxy Laboratories Limited**, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a. 12 June 03
(MANISH CHAWLA)

b.
(RAJEEV SINGH RAGHUVANSHI)

c.
(ASHOK RAMPAL)

10. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

11. Followings are the attachment with the application:
    a. Complete Specification (3 copies)
    b. Drawings (3 copies)
    c. Priority document(s)
    d. Statement and Undertaking on FORM – 3
    e. Power of Authority (Not required)
    f. Fee Rs.3,000/- (Rupees Three Thousand only..) in cheque bearing No. dated : drawn on

We request that a patent may be granted to us for the said invention.

Dated this **13TH** day of **June, 2003.**

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
Company Secretary

The present invention relates to extended release unit dosage formulations of metformin or its pharmaceutically acceptable salt thereof and the process for their preparation.

Extended release pharmaceutical dosage forms have received much attention in recent years and are highly desirable for providing a constant level of pharmaceutical agent to a patient. The nature of the delivery system is dictated by the properties and dose of the drug, desired release profile and physiological factors. For example, it would prove challenging to develop an extended release system for a high dose, water-soluble drug with a narrow absorption window limited to either stomach and/or the upper intestine.

Extended release dosage forms not only increase patient compliance due to reduction in frequency of dosing, but they also reduce the severity and frequency of side-effects, as they maintain substantially constant blood levels and avoid fluctuations associated with the conventional immediate release formulations.

Metformin has been widely prescribed for lowering blood glucose in patients with non-insulin dependent diabetes mellitus (NIDDM). However, being a short acting drug, metformin requires twice (bid) or three times-a-day (tid) dosing. A clear advantage of an extended release dosage form would be a reduction in the frequency of administration.

Adverse events associated with metformin use are often gastrointestinal, e.g. anorexia, nausea, vomiting and occasionally diarrhoea, etc. These adverse effects may be partially avoided by reducing the initial and / or maintenance dose or using an extended release dosage form.

Metformin has intrinsically poor permeability in the lower portion of the gastrointestinal tract leading to absorption from the upper part of the tract. It has very high solubility in water (>300mg/ml at 25°C). These parameters can lead to difficulty in providing a sustained release of the drug from a formulation and the concomitant problems associated with controlling the initial burst from such a formulation. The rate of dissolution of such high solubility drugs may be reduced by

FORM 2

0605-DEL-03

16 JUN 2003

The Patents Act, 1970

(39 of 1970)

COMPLETE SPECIFICATION

(See Section 10)

A PROCESS FOR THE PREPARATION OF CONTROLLED RELEASE TABLETS OF METFORMIN

ORIGINAL

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

embedding the drug in a polymeric matrix or surrounding it with a polymeric barrier membrane through which the drug must diffuse to be released for absorption.

The approaches may be beneficial for low dose drugs as large amounts of polymers are required but not for those drugs that are administered in daily doses of the order of many hundreds of milligrams.

Metformin hydrochloride is commercially available under the brand name Glucophage (conventional) and Glucophage XR (extended release tablets), currently marketed by Bristol Myers Squibb. Glucophage conventional tablets contain 500 mg, 850 mg and 1000 mg of metformin hydrochloride. Glucophage XR tablets (500 mg metformin hydrochloride; extended release) comprise a dual hydrophilic matrix system which is covered by US patent 6,475,521, which describes a method for preparing a biphasic controlled release delivery system adapted for delivery of metformin. It describes a two phase system which includes an inner solid particulate phase containing the drug and an extended release material and an outer solid continuous phase containing extended release material. On coming in contact with the release medium, the drug released from the particles of the inner phase, migrates through the outer solid continuous phase and is then released into the upper gastrointestinal tract.

However, the total tablet weight of each tablet containing 500mg of the active ingredient is about 1000 mg, as substantial amounts of polymers are required for controlling the rate of drug release. A scale-up formulation containing 1000mg drug, when made according to this invention would weigh at least 2 g. This would be unacceptably large for human consumption, and two tablets of 500mg strength each would be required for administering the daily adult dose of 1000mg metformin.

Metformin is a highly water soluble drug having poor flow and compressibility characteristics, hence, cannot be compressed in its pure form. Moreover, it is a high dose drug and therefore the tendency for capping is particularly high during the production of tablets. This capping results not only in loss of yield but also impairment of the quality. The high drug content leaves little scope to play with the excipients.

Attempts have been made to obtain directly compressed tablets by compressing drug and suitable excipients, which aid in processing and improve the properties of the product. However, direct compression is usually limited to those situations where the drug has a crystalline structure and physical characteristics required to form pharmaceutically acceptable tablets. But, in cases where the active ingredient is not compressible directly, one or more excipients must be added. Since each excipient added to the formulation necessarily increases the tablet size, direct compression method is limited to formulations containing a low dose active ingredient. Moreover, the tendency for capping is particularly high in case of directly compressed tablets containing high doses of active ingredient.

One such attempt was made in US Patent No. 6,117,451 which describes the use of specific excipients of particular size and density range to improve the flow and compressibility of metformin hydrochloride. These excipients are blended with metformin and the blend is then directly compressed.

Wet granulation method is used to convert a powder mixture into granules having suitable flow and cohesive properties for tabletting. The process involves mixing the powders in a suitable blender followed by adding the granulating fluid under shear to the mixed powders to obtain a granulation. The damp mass is then screened through a suitable screen and dried. The wet granulation process may also result in variable release characteristics depending on the degree of hydration of the polymer. Even the fluid volume of the granulating agent and granulating time may also affect the release characteristics. Further, use of organic solvent leads to the problem of residual solvent.

US Patent No. 5,955,106 discloses a process comprising granulating metformin and a hydrocolloid forming retarding agent with an aqueous solvent to form a granulated product and drying the granulated product. The hydrocolloid forming agents on coming in contact with aqueous medium, swell and form a gel matrix which erodes to release the drug.

Extended release compositions of metformin have also been formulated using other techniques. US Patent NO. 6,340,475 describes oral dosage forms in which the

drugs are incorporated into polymeric matrices comprised of hydrophilic polymers that swell upon imbibition of water to a size that is large enough to promote retention of the dosage form in the stomach. The swollen polymeric matrix remains intact long enough for substantially all of the drug to be released before dissolution of the matrix occurs.

However, there is still a need for a dosage form for metformin, which is capable of incorporating a high dose, is simple to manufacture and provides extended release. Also there is a necessity for a process which is capable of imparting good flow and compressibility characteristics to the blend, solves the problem of capping and provides the desired extended release as well.

We have now discovered that an extended release pharmaceutical composition of metformin, which maintains therapeutic blood level concentrations of the medicament in a patient for sufficiently long time, can be formulated as a monolithic matrix , which slowly releases the active agent over a prolonged period of time.

According to one aspect, extended release metformin tablets are formulated as a monolithic matrix comprising metformin, rate-controlling polymers and other pharmaceutically acceptable excipients.

According to yet another aspect, the extended release metformin tablets are provided which can incorporate a high dose of metformin and are of acceptable size, making it convenient for oral administration.

In another aspect, the extended release metformin tablet comprises a monolithic system that delivers highly soluble metformin at a relatively constant rate over extended periods of time and is easy to manufacture.

According to yet another aspect, extended release metformin tablets are provided which comprise 5-25% w/w of rate controlling polymers. The use of less amount of rate controlling polymers ensures that the total weight of the dosage form is low and a single dosage unit is sufficient to provide the therapeutic dosage of the drug.

Thus, extended release tablets provide obvious benefits with respect to better patient convenience and patient compliance.

It is one of the aspects to provide extended release metformin tablets which release metformin in a controlled manner over a time period of 24 hours, particularly over 12 hours.

According to yet another aspect, there is provided an extended release metformin tablets of 850 mg strength comprising metformin, 5-25% w/w of rate-controlling polymers and other pharmaceutically acceptable excipients.

According to yet another aspect, there is provided an extended release metformin tablets of 1000 mg strength comprising metformin, 5-25% w/w of rate-controlling polymers and other pharmaceutically acceptable excipients.

It is one general aspect to provide monolithic extended release tablets comprising not less than 500 mg metformin, wherein the total weight of the tablet does not exceed 1500 mg.

In another general aspect, a process is provided for preparing extended release tablets of metformin or non-toxic acid addition salts thereof, which comprises blending of the ingredients followed by roller compaction or slugging. The compacts are suitably sized and compressed to form tablets.

In another general aspect, a process for preparing extended release metformin tablets of 850 mg strength by roller compaction is provided.

In another general aspect, a process for preparing extended release metformin tablets of 1000 mg strength by roller compaction is provided.

Roller compaction generally involves a screening procedure that can lead to a narrower particle size distribution with fewer particles at either extreme of the size range. Roller compaction provides several other advantages, for example, uniform

blends are produced with uniform particle size range, flow properties are improved, aids in dust control, increases bulk density and controls particle hardness.

It is yet another aspect to provide extended release metformin tablets of higher strengths, comprising:

a. more than 500 mg metformin,
b. 5-25% w/w rate controlling polymer(s), and
c. other pharmaceutically acceptable excipients.

According to another aspect, a process for preparing extended release metformin tablets comprises:

(a) blending metformin, 5-25% w/w of rate controlling polymers and other pharmaceutically acceptable excipients,
(b) compacting / slugging,
(c) milling or crushing the compacted / slugged material of step (b) into granules,
(d) lubricating and compressing the granules to form tablets.

According to our co-pending Indian patent application, 1002/DEL/2001 which is incorporated herein by reference, metformin may be moisture conditioned before blending with rate controlling polymers and other excipients to further improve the flow properties. Alternatively, metformin may be blended with the rate controlling polymers and/or other excipients and then moisture-conditioned.

Accordingly, a process for preparing extended release metformin tablets comprises:

a. moisture conditioning metformin,
b. blending with 5-25% w/w of rate controlling polymers and other pharmaceutically acceptable excipients,
c. compacting / slugging,
d. milling or crushing the compacted / slugged material of step (b) into granules,
e. lubricating and compressing the granules to form tablets.

Accordingly, another process for preparing extended release metformin tablets comprises:

a. blending metformin, 5-25% w/w of rate controlling polymers and other pharmaceutically acceptable excipients,
b. moisture conditioning the blend,
c. compacting / slugging,
d. milling or crushing the compacted / slugged material of step (b) into granules,
e. lubricating and compressing the granules to form tablets.

According to one of the embodiments, a process for preparing metformin extended release tablets is provided, wherein the tablets have better strength, aesthetic appeal, desired profile and yield and are capable of incorporating very high doses of the drug, without making them unacceptably large to swallow.

While not intending to be limited by any theory, it is believed that upon oral ingestion of the extended release tablets, in an aqueous environment, such as the stomach, water penetrates the matrix and swelling takes place. As a consequence, polymer chains relax and the active ingredient begins to diffuse out from the swollen layer. Release rate is a function of the rate of uptake of water from the surrounding media and the rate of drug diffusion. The main element of the mechanism of drug release is the gel layer which is formed around the matrix. The gel layer is capable of preventing matrix disintegration and further aid water penetration. Finally, drug release is controlled by drug diffusion through the gel layer.

Metformin can be used in the form of acid addition salts of inorganic or organic acids. These acids are exemplified by, but are not limited to, acids such as hydrochloric acid, formic acid, acetic acid, malic acid, tartaric acid or fumaric acid.

Metformin constitutes up to 1000 mg per tablet.

Rate controlling polymers may be selected from the group consisting of cellulose derivatives, starch or its derivatives, alginates, acrylic and methacrylic acid derivatives, polyethylene oxides, gums and carbohydrate based polymers.

Cellulose derivatives may be selected from the group consisting of ethyl cellulose, methyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxymethylcellulose, hydroxypropyl methyl cellulose and sodium carboxy methyl cellulose of different degrees of substitution and molecular weights. These polymers may be used alone or in combination.

The acrylic acid polymers may be carboxy vinyl polymers such as those available under the brand name Carbopol (B.F. Goodrich, USA).

Carbohydrate based polymers may be selected from amongst xanthan gum, tragacanth gum, gum karaya, guar gum, acacia, gellan gum, locust bean gum and the like.

Rate-controlling polymers constitute 5-25% w/w of the formulation.

The pharmaceutically acceptable excipients may be selected from amongst diluents, binders, lubricants, glidants and flavouring agents which are physically and chemically compatible with metformin and which would help in optimizing tablet hardness, friability, drug dissolution and the production process.

Diluents may be selected from any such pharmaceutically acceptable excipients, which give bulk to the composition and improve compressibility. These may be selected from starch and starch derivatives, dicalcium phosphate, calcium sulphate, sorbitol, microcrystalline cellulose, lactose, glucose, mannitol, alginates, alkali earth metal salts, clay or polyethylene glycols.

Binders may be selected from starch, mannitol, polyvinyl pyrrolidone, carboxymethyl cellulose, hydroxy alkyl celluloses, dextrin, carbohydrate gums, alginates, polyacrylic acid, polyvinylalcohol or mixtures thereof.

Lubricants may be selected from talc, magnesium stearate, other alkali earth metal stearates like zinc, calcium stearate etc; sodium lauryl sulphate, hydrogenated vegetable oil, sodium benzoate, sodium stearyl fumarate, glyceryl monostearate and polyethylene glycol.

Glidants may be selected from colloidal silicon dioxide and talc.

The blend is compacted by roller compaction. Alternatively, this blend could be compressed to make slugs. One of the embodiments includes compaction or slugging of metformin either alone or after blending with rate controlling polymers and/or with excipients.

The compacted / slugged material is crushed / milled by a suitable milling machine like oscillating granulator / multimill / Fitzmill and sieved into the desired granule size.

These granules are lubricated with the lubricant and compressed into tablets.

If desired metformin may be mixed with one or more other antidiabetic agents prior to the compaction step. Suitable antidiabetic agents include antidiabetic agents selected from the group consisting of sulfonylureas (e.g., glyburide, glipizide, glimepiride, glipyride, chlotpop de and gliciazide), .alpha.-glucosidase inhibitors (e.g., acarbose and miglitol; and glitazones (e.g., rosiglitone and pioglitzone) as well as combinations of two or more of the foregoing antidiabetic agents.

The following examples illustrate various embodiments and they are not to be construed to limit the claims in any manner.

EXAMPLE 1

Ingredients	Weight (mg) per tablet
Metformin hydrochloride	1000.00
Sodium Carboxymethyl cellulose	25.00
Microcrystalline cellulose	85.00
Hydroxypropyl methyl cellulose	275.00
Magnesium stearate	3.75
Colloidal Silicon Dioxide	16.25
Water	45.00
Total	**1450.00**

Process:

1. The ingredients were weighed and sifted through suitable sieves.
2. Metformin hydrochloride and microcrystalline cellulose were mixed in a blender and sprayed with required quantity of purified water.
3. The blend of step 2 was mixed with sodium carboxymethylcellulose, hydroxypropyl methyl cellulose, magnesium stearate and a part of colloidal silicon dioxide.
4. The mass of step 3 was sifted and then compacted using a roller compactor.
5. Compacted material was suitably sized.
6. Sized granules were lubricated and compressed into tablets.

EXAMPLE 2

Ingredients	Weight (mg) per tablet
Metformin hydrochloride	850.00
Sodium Carboxymethyl cellulose	21.25
Microcrystalline cellulose	72.25
Hydroxypropyl methyl cellulose	233.75
Magnesium stearate	3.1875
Colloidal Silicon Dioxide	13.8125
Water	38.25
Total	**1232.5**

Process: As given for Example 1.

The release profiles of tablets prepared according to Example 1 and 2 are provided in Table 1.

Table 1: Release profile of tablets of Example 1 and 2 in pH 6.8 phosphate buffer / 900ml/USP Apparatus II/50 rpm.

Time (hr)	Per cent drug release (%) from tablets of Example 1	Per cent drug release (%) from tablets of Example 2
0.5	23	21
1.0	33	30
2.0	46	45
4.0	63	66
6.0	76	79
8.0	85	87
10.0	91	95
12.0	94	96

EXAMPLE 3

Ingredients	Weight (mg) per tablet
Metformin hydrochloride	1000.00
Sodium Carboxymethyl cellulose	25.00
Microcrystalline cellulose	36.50
Hydroxypropyl methyl cellulose	325.00
Magnesium stearate	3.00
Colloidal Silicon Dioxide	15.5
Water	45.00
Total	**1450.00**

Process: As given for Example 1.

EXAMPLE 4

Ingredients	Weight (mg) per tablet
Metformin hydrochloride	1000.00
Dicalcium phosphate	205.00
Hydroxypropyl methyl cellulose	175.00
Magnesium stearate	5.00
Colloidal Silicon Dioxide	10.00
Talc	5.00
Water	20.00
Total	**1420.00**

Process: As given for Example 1.

The release profiles of tablets prepared according to Example 3 and 4 are provided in Table 2.

Table 2: Release profiles of tablets of Example 3 and 4 in pH 6.8 phosphate buffer / 900ml/USP Apparatus II/50 rpm.

Time (hr)	Per cent drug release (%) from tablets of Example 3	Per cent drug release (%) from tablets of Example 4
0.5	18	21
1.0	28	31
2.0	41	47
4.0	59	67
6.0	70	80
8.0	79	90
10.0	86	94
12.0	88	96

WE CLAIM:

1. A process for preparing extended release metformin tablets of higher strengths, comprising:
    a. more than 500 mg metformin,
    b. 5-25% w/w rate controlling polymer(s), and
    c. other pharmaceutically acceptable excipients.
2. The process according to claim 1 wherein the extended release tablets comprise not less than 850 mg metformin.
3. The process according to claim 1 wherein the extended release tablets comprise not less than 1000 mg metformin.
4. The process according to claim 1 wherein metformin may be selected from base *per se* or a pharmaceutically acceptable salt thereof.
5. The process according to claim 4 wherein the pharmaceutically acceptable salt is hydrochloride, fumarate, hydrobromide, succinate or embonate.
6. The process according to claim 5 wherein the pharmaceutically acceptable salt is hydrochloride.
7. The process according to claim 1 wherein rate controlling polymers may be selected from the group consisting of cellulose derivatives, starch or its derivatives, alginates, acrylic and methacrylic acid derivatives, polyethylene oxide, gums and carbohydrate based polymers.
8. The process according to claim 7 wherein the rate controlling polymer is a cellulose derivative.
9. The process according to claim 8 wherein the cellulose derivative is selected from the group consisting of ethyl cellulose, methyl cellulose, hydroxymethyl cellulose, hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, sodium carboxymethylcellulose or mixtures thereof.
10. The process according to claim 9 wherein the cellulose derivative is a combination of hydroxypropyl methyl cellulose and sodium carboxymethyl cellulose.
11. The process according to claim 1 wherein the other pharmaceutically acceptable excipients comprise diluent, binder, lubricant, glidants and flavouring agents.

12. The process according to claim 11 wherein the diluent is microcrystalline cellulose.
13. The process according to claim 11 wherein the lubricant is magnesium stearate.
14. The process according to claim 11 wherein the glidant is colloidal silicon dioxide.
15. The process according to claim 1 comprises:
    a. blending metformin, 5-25% w/w rate controlling polymers and other pharmaceutically acceptable excipients,
    b. compacting / slugging,
    c. milling or crushing the compacted / slugged material of step (b) into granules,
    d. lubricating and compressing the granules to form tablets.
16. The process according to claim 15 wherein tablets are prepared by compaction.
17. The process according to claim 16 wherein tablets are prepared by roller compaction.
18. The process according to claim 1 wherein the total tablet weight is not more than 1500 mg.
19. The process according to claim 1 wherein the tablets release metformin in a controlled manner over 24 hours.
20. The process according to claim 19 wherein the tablets release metformin over 12 hours.
21. The process of claim 1 further comprising mixing metformin with an antidiabetic agent selected from the group consisting of sulfonylureas; alpha-glucosidase inhibitors; glitazones and combinations of two or more of the foregoing antidiabetic agents.
22. A process for preparing metformin hydrochloride extended release tablets as described and illustrated by the examples herein.

Dated this **30TH** day of **MAY, 2003.**

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

ABSTRACT

The present invention relates to extended release unit dosage formulations of metformin or its pharmaceutically acceptable salt thereof and the process for their preparation. The extended release metformin tablets of the present invention can incorporate a high dose of metformin and are of acceptable size, making it convenient for oral administration.